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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,375	02/02/2007	Peter F. Muhlradt	03100262AA	3623

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EXAMINER	
JUEDES, AMY E	
ART UNIT	**PAPER NUMBER**
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,375	MUHLRADT ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,25-27 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 25-27, and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 12/7/09, are acknowledged.

Claims 28-29 and 33-38 have been cancelled.

Claims 10, 25, 27, and 32 have been amended.

Claims 10, 25-27, and 30-32 are pending and are under examination.

2. In view of Applicant's amendment to the claims, only the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 25-27, and 30-32 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of "IFN-gamma variants".

As set forth previously, The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Even when the claims are limited to "variants" of IFN-gamma, this still might encompass a broad range of different polypeptides or peptides. The specification does not disclose a correlation between the structure of IFN-gamma variants, and their ability to act as agonists for the INF-gamma receptor. Likewise, there is no art recognized

correlation between said structure and function. Furthermore, the instant specification only discloses a single species of IFN-gamma receptor agonist (IFN-gamma) and does not disclose any IFN-gamma "variants". This is not representative of the broad range of structurally different "variants" encompassed by the instant claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

Applicant's arguments filed 12/7/09 have been fully considered, but they are not persuasive.

Applicant argues that the amendment to the claims to limit the variants to those that bind to the IFN-gamma receptor obviates the rejection.

However, as noted above, the specification does not provide any correlation between the structure and function of IFN-gamma variants capable of binding IFN-gamma receptor, nor does it disclose a single species of variant. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus of IFN-gamma variants.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
>
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 10, 25-27, and 30-32 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO 03/022215, as evidenced by Farhat et al., 2008, and Heldewein et al., 2003.

As set forth previously, WO 03/022215 teaches compositions comprising dendritic cells that are obtained by culturing said dendritic cells in the presence of BCG and IFN-gamma (see page 4 in particular). WO 03/022215 also teaches compositions comprising said dendritic cells co-cultivated with autologous T lymphocytes, including for 24 hours (see pages 6, 17, and 23, in particular). WO 03/022215 also teaches loading said dendritic cells with antigen (see page 4, in particular). WO 03/022215 also teaches that the dendritic cells are suitable for inducing a Th1 response (see page 6, in particular). WO 03/022215 also teaches that the dendritic cell compositions can be administered to a subject in need of immunostimulation (i.e. as a therapeutic composition, see page 17-18 in particular). WO 03/022215 also teaches monocyte derived dendritic cells (see page 5 in particular). WO 03/022215 teaches using the dendritic cells for injection into a tumor (i.e. dendritic cell composition "adaptable as a vaccine for the treatment of malignancies", see page 18, in particular). WO 03/022215 also teaches washing the dendritic cells extensively and resuspending the cells in X-VIVO medium (i.e. a physiological medium, see page 23 in particular). Furthermore, as evidenced by Heldewein et al., BCG is a TLR2 agonist (see page 284, in particular). Additionally, as evidenced by Farhat et al., ligands that signal through TLR2 or TLR2/TLR6 heterodimers (i.e. TLR2 and TLR6 agonists) induce an identical signaling pathway and gene expression profile (see page 693, in particular). The instant claims are drawn to a product, a dendritic cell, and the patentability of a product does not depend on its method of production (see MPEP 2113). Therefore, the product by process limitations of the instant claims wherein the dendritic cells are produced using a particular TLR2/TLR6 agonist does not distinguish the dendritic cells from those of WO 03/022215, since all TLR2 or TLR2/6 agonists would induce identical signaling pathways and gene expression profiles (i.e. would result in dendritic cells with identical properties). Thus, even though the dendritic cells of WO 03/022215 have been produced by a method different than that of the instant claims (i.e. culture with IFN-gamma and a TLR2 agonist, instead of IFN-gamma and a TLR2/TLR6 agonist such as MALP-2), they are structurally identical to the TH1 inducing dendritic cells of the instant claims.

Applicant's arguments filed 12/7/09 have been fully considered, but they are not persuasive.

Applicant argues that BCG acts via TLR2 and TLR4, in contrast to the bisacyoxypropyl derivative of the instant claims, which does not activate TLR4. Thus, Applicant concludes that BCG and a bisacyoxypropyl derivative are not the same.

As conceded by Applicant, BCG stimulates TLR2, which induces an identical signaling pathway as a TLR/TLR6 agonist. The fact that BCG might also stimulate TLR4 is not relevant, since the claims are not limited to a dendritic cell produced in the presence of a TLR2 agonist and not a TLR4 agonist (i.e. the claims encompass dendritic cells produced by stimulating TLR2/TLR6 and TLR4). The dendritic cells of WO 03/022215 have been made by inducing the same intracellular signaling pathways (i.e. TLR2/TLR6 and IFN-gamma receptor) as those recited in the instant claims.

Furthermore, the instant claims are drawn to a product, and the patentability of a product does not depend on its method of production. In the instant case, the dendritic cells of WO 03/022215 are structurally identical to those of the instant claims, since WO 03/022215 teaches that the dendritic cells acquire the property to drive T helper cell type 1 responses, as recited in the instant claims.

Applicant further argues that the combination of a TLR2/TLR6 agonist and IFN-gamma results in a synergistic effect, and that both are required to produce a Th1 inducing dendritic cells. Applicant notes that only the present invention is able to achieve a dendritic cell having acquired the property to drive a Th1 response.

WO 03/022215 teaches that BCG (which inherently comprises a TLR2/TLR6 agonist) and IFN-gamma act synergistically to induce IL-12p70 producing dendritic cells capable of driving a Th1 response (see pages 20-23). Thus, WO 03/022215 teaches a dendritic cell identical to that of the instant claims, though produced by a different method.

Applicant further argues that WO 03/022215 does not teach treatment of allergic disorders.

The treatment of allergic disorders refers to an intended use of the claimed dendritic cells, and does not render the instant claims patentably distinct in the absence of a structural difference. The dendritic cells of WO 03/022215 produce high levels of IL-12 p70 and drive T helper 1 response, and would thus inherently be capable of treating allergic disorders, as recited in the instant claims.

6. Claims 10 and 25-27 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Re et al., 2001 (of record).

As set forth previously, Re et al. teach a composition comprising dendritic cells that are obtained by culturing said dendritic cells in the presence of peptidoglycan (PGN) and IFN-gamma (see page 37698 and Fig. 5, in particular). Re et al. also teach that PGN is an agonist of TLR2 and TLR6 (see page 37696, in particular). Re et al. teach that the dendritic cells produce IL-12, which induces TH1 polarization (see page 37698 and Fig. 5, in particular). Re et al. teach monocyte derived dendritic cells (see page 37693, in particular). Furthermore, the TLR2/TLR6 agonist of Re et al. can be considered a "derivative" of bisacyloxypropyl-S-cystein or of MALP-2, since it stimulates the same TLR receptors. Furthermore, even if the TLR2/TLR6 ligand of Re et al. is different than those of

the instant claims (for example, those recited in claim 27), the instant claims are drawn to a product, and the patentability of a product does not depend on its method of production. The PGN taught by Re et al. stimulates the exact TLR receptors recited in the instant claims, and would thus result in a dendritic cell with identical properties irrespective of the particular TRL2/TLR6 agonist used. Furthermore, regarding the limitation of a "therapeutical composition", it is noted that this refers to an intended use of the dendritic cell compositions and does not carry patentable weight in the absence of a structural different in the product. Re et al. disclose a composition comprising TLR2/TLR6 agonist and IFN-gamma receptor matured dendritic cells in RPMI 1640 medium (see page 37695 in particular). Tissue culture medium is compatible with physiologic conditions, and not incompatible with a therapeutic use. Additionally, the instant specification on pages 4-5 discloses that agonists added to a culture of dendritic cells can be used as a therapeutic composition as such. Re et al. disclose said agonists added to a culture of dendritic cells. Thus, based in the teachings of the instant specification, the cell compositions taught by Re et al. are structurally identical to the "therapeutic" composition of the instant claims.

Applicant's arguments filed 12/7/09 have been fully considered, but they are not persuasive.

Applicant argues that, as evidenced by Travassos et al., the PGN used by Re et al. was contaminated with LPS, and therefore acted as a TLR2 and a TLR4 agonist.

The PGN used by Re et al. was isolated from *Staphylococcus aureas*, a gram positive bacteria that does not even comprise LPS. Additionally, Re et al. specifically demonstrate that the PGN preparation acts only as a TLR/TLR6 agonist, and not as a TLR4 agonist (see Fig. 1A, in particular). Furthermore, in contrast to Applicant's assertion, Travassos et al. does not demonstrate that PGN preparations are contaminated with LPS, but rather demonstrate that PGN can be contaminated with lipoteichoic acid or lipopeptides (i.e. bisacyloxypropyl "derivatives" that acts as a TLR2/TLR6 agonist). Thus, the PGN preparation used by Re et al (even if contaminated with lipopeptides) is a TLR2/TRL6 agonist and not a TLR4 agonist. Thus, the dendritic cells of Re et al. have been produced by stimulation with IFN-gamma and a TLR2/TLR6 agonist (i.e. PGN). Further, Re et al. teach that the combination of the PGN and IFN-gamma act synergistically to induce IL-12 p70 production by the dendritic cells (i.e. the dendritic cells of Re et al. are capable of driving a Th1 response, see Fig. 5, in particular). Thus, the dendritic cells of Re et al. are structurally identical to those of the instant claims, despite their method of production (i.e. with cultured with PGN as the TLR2/TLR6 agonist, instead of the agonists recited in claim 27, for example).

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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